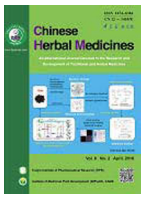

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## Review

# Advances in Study on Three-dimensional Printing in Pharmaceutics

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ABSTRACT

Three dimensional printing (3DP) is a solid freeform fabrication technology which employs powder processing and a liquid binder material in the construction of parts in a layer-wise manner. 3DP can accommodate much geometric outline and be made with many materials due to its unprecedented flexibility. The technology can control over the material composition, microstructure and surface texture so it attracts great attentions in the pharmaceutics field. 3DP can offer many novel strategies and approaches for the research and is widely focused in the field of the controlled-release drug delivery systems. Through consulting a large number of documents the current development and the technical characteristics of 3DP in pharmaceutics field are discussed and reviewed. It is expected that 3DP technique may play a tremendous role in pharmaceutics field in the future.

*Key words*

controlled-release drug delivery; excipient; pharmaceutics; three dimensional printing

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## 1. Introduction

In the late 1980s, the rapid prototyping (RP) technology was present in the United States, and the emergence and development of three-dimensional printing (3DP) technology have attracted more and more attention in the pharmaceutics field (Petezold et al, 1999). In its most basic step, people use computer-aided drafting technology and programming to produce a 3D object by layering material onto a substrate. The 3DP method utilizes ink-jet printing technology to create a solid object by printing a binder into selected areas of sequentially deposited layers of powder. As shown in Figures 1 and 2, the 3DP machine is composed of a pair of horizontal X-Y axis that are suspended over a vertical piston, providing control over three directions of motion. The process begins by spreading a thin layer of powder onto a piston plate. A liquid binder solution passed through a nozzle affixed to the fast-axis carriage, and the nozzle is restored back and forth over the powder bed to selectively print droplets which bind the powder particles together, generating a 2D pattern. The piston is dropped a fixed distance, another thin layer of powder is spread. This process is repeated following the computer-aided drafting instructions until the object is built layer by layer. After treatment to remove the unbound substrate, the object is complete (Rowe et al, 2000; (Sastry et al, 2000; Ursan et al, 2013). Since the process was first described, 3DP has been used in many fields such as architecture, medicinal, chemical, biomedical, and pharmaceutical manufacturing (Yu et al, 2005; Hutmacher et al, 2007; Symes et al, 2012; Sandler et al, 2014; Goyanes et al, 2014).

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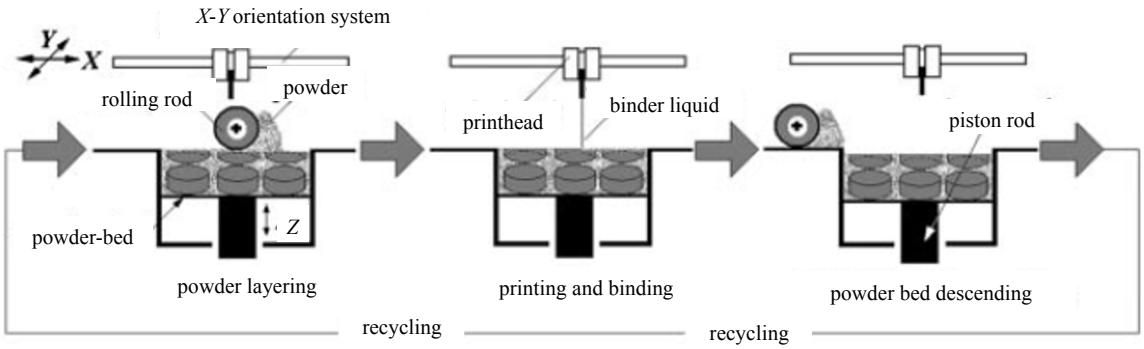


**Figure 1 Schematic diagram of 3DP (Yu et al, 2009)**

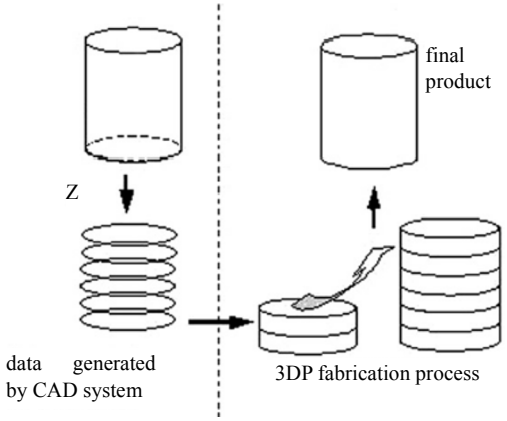


**Figure 2 Schematic illustration of 3DP principle**

## 2. Matrix (excipient)

3DP technology consisted of two major elements, binding liquid and matrix. The binding liquid and matrix were selected according to the requirement of the experiment. Preparation of a medicine formulation with 3DP technology also needs to rely on a variety of polymers as carriers (Pillai et al, 2001). In the tablets, the microcrystalline cellulose, HPMC are commonly used as matrix. In the implants, due to the presence of HPMC, the implants may crack after swelling, so it generally not be used. Poly-ε-caprolactone (PCL), polylactic acid (PLA), polyglycolide (PLG), polylactide glycolide (PLGA), etc are more used.

In the practical application, the matrix material is often a mixture composed of various materials.

### *2.1 Tablet*

Monkhouse et al (2000) fabricated an oral fast-dispersible tablet, the lactose content of which is 95% and the content of PVP Kollidon 25 is 5%, drug released only a few seconds. Pryce et al (2003) had developed an oral controlled-release dosage forms zero-order release drug delivery devices (DDD), when lactose and hydroxypropyl methylcellulose (HPMC) ratio was 80:20, the drug had been released in 15 h; when the ratio changed to 70:30, drug released in 36 h. Goyanes et al (2015) selected 5-aminosalicylic acid (5-ASA, mesalazine) and 4-aminosalicylic acid (4-ASA) as model drugs, commercially produced polyvinyl alcohol (PVA) filaments as polymer filaments. They found that the FDA 3DP was an effective process for 5-ASA, but the substantial degradation of 4-ASA when 3DP used to cause the method was not suitable. The diameter of the polymer filament remained constant, and was therefore easily extruded by the printer. Khaled et al (2014) used commercial guaifenesin bi-layer tablets (GBT) (Figure 3) as a model drug, hydroxypropyl methylcellulose (HPMC 2208) and poly (acrylic acid) (PAA) were used as a hydrophilic matrix for a sustained release (SR) layer. Hypromellose® (HPMC 2910) was a binder while microcrystalline cellulose (MCC) and sodium starch glycolate (SSG) were used as disintegrants for an immediate release (IR) layer. They demonstrated all formulations through a hydrated HPMC gel layer showed Fickian diffusion drug release and achieved high drug loading. Yu et al (2007) fabricated complex tablets with zero-order drug release characteristics. They chose HPMC, ethyl cellulose (EC), Eugragit RS−100, stearic acid (SA), and sodium lauryl sulfate (SLS) as release retardation materials and evaluated their potential to modify drug release profiles in 3DP tablets. Dissolution tests showed that EC gradient tablets has acceptable mechanical and pharmacotechnical properties, 98% of the drug could be released in 12 h. Tablets with SLS, SA, and Eudragit RS−100 gradients could linearly release 79%, 97%, and 97% of the drug in 5, 10, and 13 h, respectively. Yu et al (2009) designed and fabricated novel fast-disintegrating DDD, mixed powder composed of paracetamol, lactose, PVP K30, mannitol and colloidal silicon dioxide. The results showed that the FD-DDDs had acceptable pharmacotechnical properties but the mechanical property is a limitation. Skowyra et al (2015) fabricated extended release tablet using prednisolone loaded poly (vinyl alcohol) (PVA) filaments with the fused deposition modelling (FDM) based 3D printer. They demonstrated that FDM 3D printers can be utilized to construct flexible dose tablets.

### *2.2 Implant*

Wu et al (2009) fabricated a new type of drug implant with a double-layer structure; the upper region was a reservoir system containing rifampicine (RFP) while the lower region was a matrix one containing employing levofloxacin (LVFX). And the powder of biocompatible poly-l-lactide (PLA) was

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